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Sami N. Nasrallah

University of Kentucky, sami.nasrallah@uky.edu

L. Raymond Reynolds

University of Kentucky, lrreyn2@uky.edu

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Insulin Degludec, The New Generation Basal Insulin or Just another Basal Insulin?

Sami N. Nasrallah and L. Raymond Reynolds

University of Kentucky. Corresponding author email: sami.nasrallah@uky.edu

Abstract: The advances in recombinant DNA technology have led to an improvement in the properties of currently available long-acting insulin analogs. Insulin degludec, a new generation ultra-long-acting basal insulin, currently in phase 3 clinical trials, has a promising future in clinical use. When compared to its rival basal insulin analogs, a longer duration of action and lower incidence of hypoglycemic events in both type 1 and type 2 diabetic patients has been demonstrated.^{1,2} Its unique mechanism of action is based on multihexamer formation after subcutaneous injection. This reportedly allows for less pharmacodynamic variability and within-subject variability than currently available insulin analogs, and a duration of action that is over 24 hours.³ The lack of proof of carcinogenicity with insulin degludec is yet another factor that would be taken into consideration when choosing the optimal basal insulin for a diabetic individual.⁴ A formulation of insulin degludec with insulin aspart, Insulin degludec 70%/aspart 30%, may permit improved flexibility of dosing without compromising glycemic control or safety.⁵

Keywords: insulin degludec, basal insulin, insulin analogs, insulin degludec 70%/aspart 30%, long-acting insulin analogs

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Introduction

Pancreatic beta cells release insulin continuously between meals at a near constant rate and in the fasting state. This basal insulin secretion acts to restrain the release of glucose from the liver and free fatty acids from the adipose tissue in order to prevent hyperglycemia and ketosis. The development of insulin analogs, in effort to produce safer insulin formulations that would closely mimic the basal and mealtime components of endogenous insulin secretion, allowed for more flexible treatment regimens with a lower risk of development of hypoglycemia. Insulin analogs, created via recombinant DNA technology, are modified versions of human insulin that primarily alter the duration of absorption of the molecule. An improvement in the properties of currently available long-acting insulin analogs has been achieved with the new generation long-acting basal insulin analog, insulin degludec. Clinical trials have demonstrated a longer duration of action and lower incidence of hypoglycemic events in both type 1 and type 2 diabetic patients using insulin degludec.^{1,2} This article reviews currently available information about insulin degludec, in comparison to the other basal insulin analogs (Table 1 and Fig. 1).

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Insulin degludec is a neutral, soluble ultra-long-acting insulin that forms large multihexamer assemblies at physiological pH following subcutaneous injection. Its molecular structure is similar to the human insulin amino acid sequence, apart from deletion of Threonine at position B30 and the addition of a 16-carbon fatty diacid attached to Lysine at position B29 via a glutamic acid spacer (Fig. 1). This conformation allows insulin

degludec to exist as dihexamers in solution which form multihexamers after subcutaneous injection.³ According to the manufacturer, Novo Nordisk, the large molecular size allows for continuous slow release of degludec monomers with reportedly less pharmacodynamic variability and within-subject variability than currently available insulin analogs, and a duration of action that is over 24 hours. Its metabolism is mainly via the kidneys. The contribution of renal metabolism is enhanced as exogenous insulin bypasses the liver.^{3,6}

A study involving 12 type 1 diabetic subjects has shown that insulin degludec had a half life longer than 24 hours and was found to be detectable in the circulation for at least 96 hours after injection; however, it is unknown whether or not it is still biologically active at that time. Insulin receptor binding studies and in vitro studies have indicated that insulin degludec is comparable to human insulin in its low affinity for the human insulin-like growth factor-1 receptor, with a similar low mitogenic/metabolic potency ratio and, therefore, no proof of carcinogenicity.^{4,6-8}

Clinical Studies

Phase 2 trials

Three phase 2 trials comparing insulin degludec with insulin glargine have been conducted. All were open-label, randomized, parallel-group, treat-to-target trials and had a duration of 16-weeks.

A trial including type 1 diabetes patients showed no differences in hemoglobin A1c, fasting plasma glucose, and mean total daily dose between insulin degludec once a day with insulin glargine once a day, both combined with insulin aspart. There was a difference in the rate of confirmed hypoglycemia and especially confirmed nocturnal hypoglycemia between insulin degludec once a day and insulin glargine once a day.

Table 1. Comparison of insulin degludec and other insulin analogs.

Basal insulin	Onset	Peak	Duration	Comments
NPH	1–2 hours	4–8 hours	8–12 hours	Greatest risk for hypoglycemia
Glargine	30–60 minutes	No peak	16–24 hours	– Greatest potential for weight gain. – Possible mitogenicity
Detemir	30–60 minutes	No peak	16–24 hours	May need twice daily injections.
Degludec	30–90 minutes	No peak	Over 24 hours	– Least risk of hypoglycemia – No mitogenicity
Degludec plus	5–15 minutes	30–60 minutes	Over 24 hours	Same as degludec with advantage of added prandial coverage.

Abbreviation: NPH, neutral protamine hagedorn.

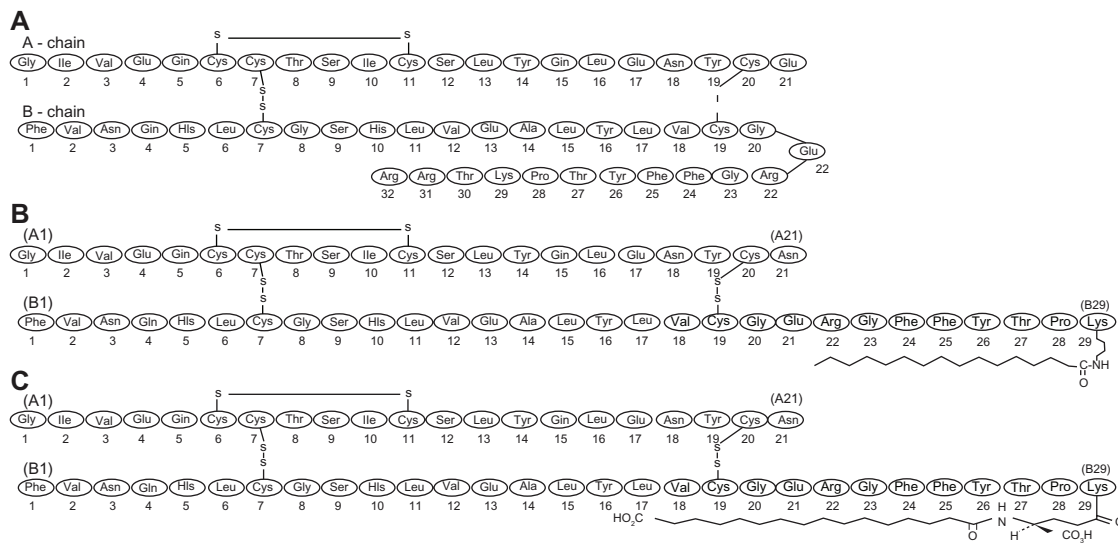


Figure 1. Molecular structure of long-acting insulin analogs: **(A)** insulin glargine, **(B)** insulin detemir, and **(C)** insulin degludec.

The rates of overall and nocturnal hypoglycemia of insulin degludec and insulin glargine and the risk reductions compared with glargine were 47.9 and 66.2 events/patient-year (relative risk 0.72) and 5.1 and 12.3 events/patient-year (relative risk 0.42), both in favor of insulin degludec once a day.^{1,9–11}

A study among diabetes type 2 patients tested insulin degludec in either a once per day regimen or a three-times weekly regimen, compared against insulin glargine. All efficacy outcome measures, including the mean weekly insulin dose, were similar compared with each other and compared with insulin glargine. This study among type 2 diabetes patients, found no significant differences in the rate of confirmed hypoglycemic events among degludec once a day, degludec three-times weekly, and insulin glargine once a day. Although hypoglycemic events occurred less with degludec once a day, they occurred more in the degludec three-times weekly treatment group.^{1,2,12} Therefore, its manufacturer, Novo Nordisk, is seeking FDA approval for once a day clinical use.

A third study investigated a Insulin degludec Plus co-formulation, comprising 70% insulin degludec and 30% insulin aspart in type 2 diabetes patients dosed at dinnertime. There was no difference in hemoglobin A1c and fasting plasma glucose compared with insulin glargine once a day.

Two outcome measures were in favor of Insulin degludec Plus compared with insulin glargine: Insulin degludec Plus had a 27 mg/dL lower mean 2-h post-dinner plasma glucose and a 7 U/kg lower mean daily

insulin dose. The rate of confirmed hypoglycemic events and nocturnal hypoglycemic events was low for both Insulin degludec Plus and insulin glargine, without significant differences between them.^{1,13,14} This co formulation is a promising treatment option for initiating insulin therapy in subjects with type 2 diabetes inadequately controlled with oral anti-diabetic agents. The phase 2 trial also investigated the use of a second formulation of insulin degludec 55%/Aspart 45%, which was associated with a twofold higher rate of confirmed, mostly nocturnal, hypoglycemia which discontinued its clinical development.¹³

In a proof-of-concept trial comparing Insulin degludec/aspart with biphasic insulin aspart 30 (30% soluble, rapid-acting insulin aspart and 70% protamine-bound insulin aspart), Insulin degludec/aspart was associated with a significantly lower fasting plasma glucose and a significantly lower rate of confirmed hypoglycemia than biphasic insulin aspart 30.¹⁵

Phase 3 studies

12 phase 3 trials are registered at www.ClinicalTrials.gov aiming to assess the efficacy and safety of insulin degludec, including approximately 7,000 participants, and all studies have been completed. Preliminary results of the phase 3 trials showed that there were no differences in A1c between Insulin degludec once a day and Insulin glargine, although Insulin degludec was not non-inferior regarding A1c when administered three-times weekly in patients with type 2 diabetes, resulting in discontinuation of the three-times



weekly dosing option. In the once a day dosing option, a reduction in nocturnal hypoglycemia was seen in a 52-week trial, together with a significantly lower fasting plasma glucose level. In one study, insulin degludec given as basal-bolus treatment with insulin aspart in people with type 2 diabetes, improved long-term glycemic control with significantly lower risk of overall and nocturnal hypoglycemia compared with insulin glargine. In patients with type 1 diabetes, Insulin degludec once a day reduced the risk of nocturnal hypoglycemia compared with Insulin glargine once a day.^{1,16} In another phase 3 trial, the efficacy and safety of Insulin degludec/aspart used once daily at any meal with insulin aspart at the remaining meals in type 1 diabetics, provided similar glycemic control to insulin detemir with mealtime insulin aspart. The Insulin degludec/aspart regimen was associated with significantly less nocturnal hypoglycemia, and had the added convenience of fewer daily injections than conventional basal-bolus therapy.¹⁷

Safety

Insulin degludec used alone is associated with less pharmacodynamic and within-subject variability than insulin glargine, with a lower chance of inducing hypoglycemia, in both type 1 and type 2 diabetic patients.^{2,9,18} The rates of hypoglycemia and nocturnal hypoglycemia, in insulin-naïve people with type 2 diabetes, were similar between insulin degludec 70%/insulin aspart 30% and insulin glargine. This lower risk of inducing hypoglycemia, in particular nocturnal hypoglycemia, might be a major factor in choosing a regimen to that targets optimal glycemic control, especially in patients with blunted hypoglycemic awareness.

In studies involving the binding affinity of insulin degludec to IGF-1 receptors, the affinity of insulin degludec for the human IGF-1 receptor was found to be low, with a molecular safety that is similar to human insulin. This has omitted any proof of carcinogenicity with insulin degludec, in comparison to concerns regarding possible metabolic and mitogenic potencies of insulin glargine.⁴

Efficacy

The continuous, slow, stable release of insulin degludec monomers provides a smooth and stable exposure for more than 24 hours, with less variability and

a more stable glucose-lowering effect than insulin glargine.^{9,19,20} Insulin degludec 70%/aspart 30% has the added advantage of a lower mean 2-h post-dinner plasma glucose increment and lower mean daily insulin dose when compared to insulin glargine.^{1,13} In one trial, it was shown that insulin degludec can be dosed flexibly at any time of the day so that injection times can be changed from day to day without compromising glycemic control or safety compared to insulin glargine dosed at the same day.⁵

Patient Preference

Based on the long duration of action and lower events of hypoglycemia and unproven carcinogenicity, the main determinant of patient preference will probably be the cost of insulin degludec given once a day.

Place in Therapy

Insulin degludec has a high potential for use as an ultra-long acting basal insulin in both the ambulatory and inpatient setting, with a more favorable profile compared to the other basal insulins currently in use. One possible disadvantage in its use in the hospital setting, due to its prolonged effect of more than 24 hours, is the decreased ability to make day-to-day adjustments in the basal insulin dose, in order to optimize blood sugar control. This potential risk may be more pronounced in patients with renal or hepatic impairment. The long acting analogs currently in use, glargine and detemir, both allow for adjustments on a daily basis or shorter period, in advent of hypoglycemia or hyperglycemia.^{8,13} However, newer clinical studies have shown that the soluble insulin combination of an ultra-long-acting basal insulin degludec and rapid-acting insulin, insulin aspart, provides fasting plasma glucose control with significantly less hypoglycemia compared to biphasic insulin aspart.²¹

Discussion

The introduction of insulin analogs has revolutionized glycemic control, through administration of basal and prandial insulin with or without “correction dose” insulin, which in turn approximates physiologic insulin demand. Insulin Lispro was the first rapid acting insulin analog, created by inversion of the lysine of B29 and the proline of B28 of human insulin, causing a conformational change that results in a shift in the normal binding of the C-terminal portion of the B

chain, which in turn reduces the formation of dimers and hexamers. In contrast, the concept behind insulin degludec, is multihexamer formation at the subcutaneous injection site which prolongs its duration of action. This mechanism of action differs from insulin degludec's predecessors, insulin glargine, which was introduced in 2001, and insulin detemir (Table 1). Insulin glargine is produced by the substitution of glycine for asparagine at position A21 of the insulin molecule and by the addition of two arginine molecules at position B30 (Fig. 1). These changes lead to a shift in the isoelectric point toward a neutral pH, which results in an insulin molecule that is less soluble at the injection site and that precipitates in the subcutaneous tissue to form a depot from which insulin is slowly released.^{7,22} Insulin detemir is an acylated derivative of human insulin which binds to albumin through a fatty-acid chain attached to the lysine at residue B29, leading to a reduction in free detemir levels (Fig. 1).

In both type 1 and 2 diabetics, the main advantage with the use of insulin glargine instead of neutral protamine hagedorn insulin "NPH", has been a reduction in the risk of hypoglycemia, especially nocturnal hypoglycemia.²² In type 2 diabetics, insulin glargine is comparable with NPH insulin, insulin detemir and exenatide in reducing A1c levels. Disadvantages of insulin glargine include weight gain versus weight loss with GLP-1 agonists and more effective A1c reduction with biphasic insulins if insulin glargine is not combined with prandial coverage.²³ A recent meta-analysis comparing the efficacy and safety of long-acting insulin analogs in patients with type 2 diabetes failing on oral therapy, demonstrated that initiating long-acting insulin analogs seems to provide glycemic control similar to rapid-acting insulin analogs or NPH insulin or glucagon-like peptide-1 analogs and slightly inferior to biphasic insulin analogs with fewer side-effects.^{22,24} Insulin detemir has less variability in absorption than does NPH, a feature associated with a reduced risk of hypoglycemia which may contribute to less weight gain (Table 1). Insulin detemir appears to have a shorter time-action profile at lower doses, compared with insulin glargine, which may require twice-daily injections in persons with type 1 diabetes.^{22,25} A recent analyses suggested that there is no clinically relevant difference in efficacy or safety between insulin detemir and insulin glargine for

targeting hyperglycemia. However, to achieve the same glycemic control insulin detemir was often injected twice-daily in a higher dose but with less weight gain, while insulin glargine was injected once-daily, with somewhat fewer injection site reactions. As with insulin glargine, similar advantages with insulin detemir include lower incidence of hypoglycemia compared with NPH and biphasic insulins²³ (Table 1).

With insulin degludec having less pharmacodynamic and within-subject variability than insulin glargine and detemir, there is a reduced chance of inducing hypoglycemia, in both type 1 and type 2 diabetic patients. Similar rates of hypoglycemia and nocturnal hypoglycemia, in insulin-naïve people with type 2 diabetes have been shown with insulin degludec 70%/insulin aspart 30% and insulin glargine.^{2,9,18}

There have been concerns of the metabolic and mitogenic potencies of insulin glargine, due to IGF-1—receptor binding and demonstration of an increase in both IGF-1—receptor affinity and mitogenic potency in a cell-culture model that used human osteosarcoma cells. This was implicated in the possible development of mammary, ovarian, and bone tumors in addition to the development of diabetic retinopathy. Due to these suspicions, it has been considered unwise to use insulin glargine in pregnancy.^{22,25} Newer data, from a large population-based follow-up study, showed that insulin glargine and users of other insulin analogs had a lower risk of cancer in general than those using human insulin; however, an increased risk of breast cancer was seen in users of insulin glargine in comparison with users of human insulin.²⁶ In a more recent cohort study involving only type 2 diabetic patients, the previous findings of an increased risk of cancer with insulin glargine compared with human insulin was not confirmed, and an increased risk of all-cause death with human insulin was found when compared with insulin glargine.²⁷ With insulin degludec, since its affinity for the human IGF-1 receptor is low, the molecular safety is similar to human insulin, with no proof of carcinogenicity (Table 1).⁴

Conclusions

The new ultra-long basal insulin degludec, which is currently still undergoing phase 3 trials, may be an attractive therapeutic alternative to the other basal insulins, due to less pharmacodynamic variability, a longer duration of action, less potential for



hypoglycemic events and lower theoretical mitogenic potential. Its developer, Novo Nordisk, has filed for regulatory approval but at this writing it still awaits approval in Europe and the US for clinical use.

Author Contributions

Wrote the first draft of the manuscript: SNN. Contributed to the writing of the manuscript: LRR, SNN. Agree with manuscript results and conclusions: LRR. Jointly developed the structure and arguments for the paper: LRR, SNN. Made critical revisions and approved final version: LRR. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contribution, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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